Synopsis of the thesis

Synthesis, Characterization & Bio-evaluation (Cytotoxic & Antibacterial activities) of Mannich & Schiff bases of Isatin and Silver Capped Nanoparticles of Isatin-3-thiosemicarbazone & N-benzoylthiourea Besides Development of Synthetic Methodology

Submitted to Andhra University for the Award of the Degree of
DOCTOR OF PHILOSOPHY

In Chemistry

Submitted by

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The thesis entitled "**Synthesis, Characterization & Bio-evaluation (Cytotoxic & Antibacterial activities) of Mannich & Schiff bases of Isatin and Silver Capped Nanoparticles of Isatin-3-thiosemicarbazone & N-benzoylthiourea Besides Development of Synthetic Methodology**"is divided into five chapters.

CHAPTER -1: Introduction & Synthetic strategies and Biological importance of Mannich bases derived from Isatins

This chapter describes introduction and previous synthetic approaches for Isatin & isatin Mannich bases and pharmacological profile of some isatin Mannich bases.

CHAPTER-2: Design, Synthesis and *invitro* Cytotoxic investigation of methyl-4-((substitutedphenyl)[6h–indolo(2,3-b)quinoxalin-6yl]methylamino)benzoate derivatives besides antibacterial studies with SAR and Docking studies

Part–A: This part of chapter consists of present work i.e., the synthesis of Mannich bases of isatin from Indoloquinoxalin

Part–B: This part of chapter consists *invitro* cytotoxic activity, antibacterial activity, SAR and docking studies of the methyl-4-((substitutedphenyl)[6h–indolo(2,3-b)quinoxalin-6yl]methylamino)benzoate.

CHAPTER-3: Efficient synthesis of Cinnamic acids and Ylidenemalononitriles via Knoevenagel condensation employing DABCO as a catalyst

Part–A: This part of chapter consists of introduction & previous synthetic approaches for cinnamic acids, ylidenemalononitriles and pharmacological profile.

Par–B: This part of chapter consists of present work including the synthesis of cinnamic acids and ylidenemalononitriles employing DABCO as a catalyst.

CHAPTER-4: Synthesis and Characterization of Isatin-3-thiosemicarbazone & N-benzoylthiourea capped silver nanoparticles by chemical reduction method and its antimicrobial activity on isolated human pathogens

Section-I:

Part-A: This part of chapter consists of introduction to nano and silver nanoparticles.

Part-B: This part of chapter consists of synthesis and characterization of isatin-3-thiosemicarbazone capped silver nanoparticles.

Part-C: This part of chapter consists of antimicrobial activity of isatin-3-thiosemicarbazone capped silver nanoparticles on human pathogens.

Section-II:

Part-A: This part of chapter consists of introduction and synthesis and characterization of N-benzoylthiourea capped silver nanoparticles.

Part-B: This part of chapter consists of antimicrobial activity of N-benzoylthiourea capped silver nanoparticles on human pathogens.

CHAPTER-5: Introduction to Schiff bases, Synthesis and Characterization of N-(4-(2-oxoindolin-3-ylideneamino)-5-(4-substitutedphenyl)-3-substitutedthiazol-2(3*H*)-ylidene) benzamide

This chapter describes introduction and previous synthetic approaches for Schiff bases and pharmacological profile of some Schiff bases including the synthesis of N-(4-(2-oxoindolin-3-ylideneamino)-5-(4-substitutedphenyl)-3-substitutedthiazol-2(3*h*)-ylidene) benzamide.

CHAPTER – 1:

Indole is an important heterocyclic unit which has special attention in the organic synthesis, due to the fact that many of its derivatives possess a variety of pharmacological properties. Indole moiety is privileged structure in numerous research areas such as pharmaceuticals, fragrances, agrochemicals, pigments, and material science. Indole chemistry received much attention when the alkaloid reserpine was introduced as one of the first drugs for the treatment of diseases of the central nervous system (CNS) such as anxiety and mental disorders. This was followed by the discovery of antitumor agent Vincristine. The diverse physiological significance of these alkaloids was expanded to anti-inflammatory, tranquilizing, and antihypertensive activities. Some of the drugs currently in market belong to the tripants which are used mainly in the treatment of migraine headaches. The potent serotonin is the one of the neurotransmitters present in the central and peripheral nervous system, which plays an important role in the normal brain function and regulates sleep, mood, appetite, sexual function, memory, anxiety etc. As a consequence enormous efforts have been made to the development of ever more efficient synthetic protocols for the preparation and direct functionalization of Indole and their fused derivatives.

Isatin (1H-indole-2,3-dione) which is a derivative of indole was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis. Isatin has been known for about 150 years and has been recently found, like oxindole and endogenous poly functional heterocyclic compounds, to exhibit biological activity in mammals. Isatin also is a synthetically versatile substrate that can be used to prepare a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis. Isatin is further known to be a color reagent for the amino acid proline, forming a blue derivative. This property has been exploited for the determination of this amino acid in pollens and other vegetable materials using paper chromatography or for the detection of polymer-bound compounds possessing proline residues.

Mannich reaction is an important tool for synthesis of novel compounds. Mannich reaction is a three-component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine. The amino alkylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds.

The gradual development of resistance to drugs by pathogenic organisms and emergence of serious side effects has been a major concern for continuation of research in discovery of new drugs. Many heterocyclic compounds of natural origin with useful medicinal properties have served as a lead compounds in designing synthetic drugs.

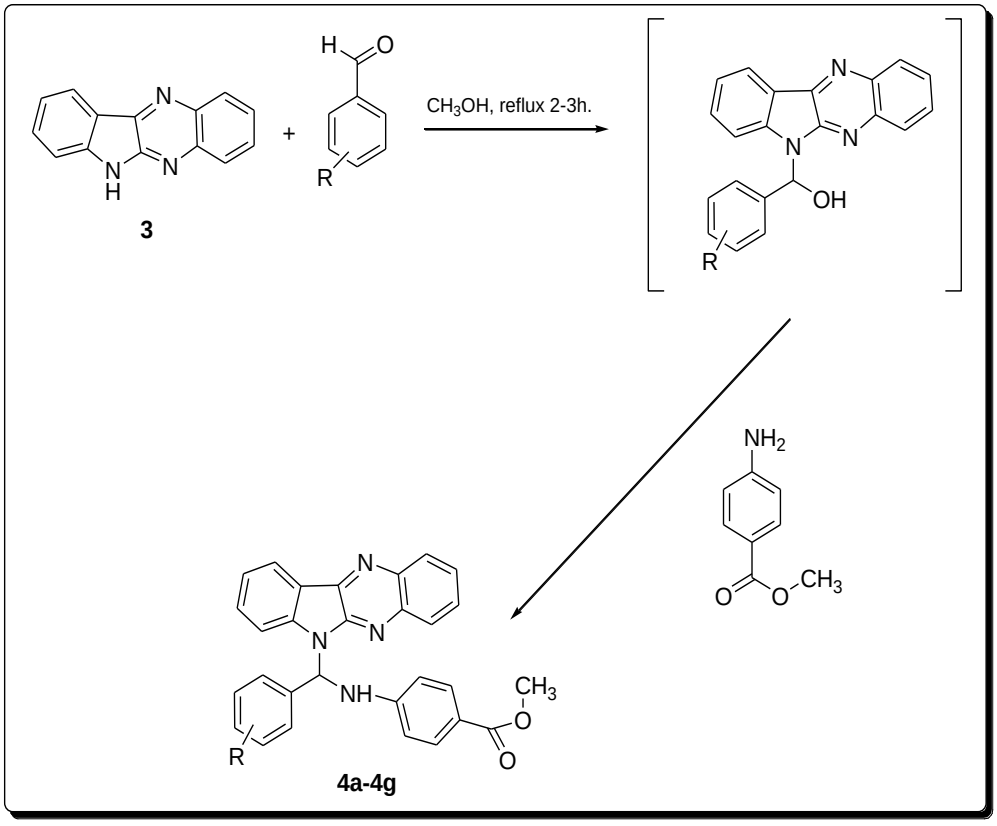
Isatin and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Isatin and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. In the past few decades, Isatin and its derivatives have received much attention due to their chemotherapeutic values. Isatin derivatives have been reported to show pharmacological actions such as antimicrobial, anticancer, antiviral, anticonvulsant, anti-inflammatory and analgesic. From these results, ideas for future molecular modifications leading to compounds with greater favorable pharmacological properties are derived.

CHAPTER–2:

PART-A:

Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as raw material for drug synthesis. Isatins have also been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions. Mannich bases of isatins are reported to exhibit broad spectrum of chemotherapeutic properties as mentioned earlier in the introduction. Hence, the research interest on isatins, isatin derivatives and Mannich bases of isatins, the present work aims at the synthesis of some indoloquinoxalins from isatin.

The present work describes the design, synthesis and antibacterial activity of newly synthesized compounds. The newly synthesized compounds are the derivatives of isatin, which are synthesized via Mannich reaction. A series of **7** compounds namely Methyl-4-((substituted phenyl)(6H-indolo(2, 3-b)quinoxalin-6yl) methyl amino)benzoate derivatives were synthesized and *invitro* cytotoxic, antibacterial activity, docking and SAR were evaluated. The synthesized compounds are characterized by elemental analysis and from spectral data like IR, ^{1}H NMR & ^{13}C NMR and mass.



Synthetic scheme

PART-B:

Cancer is undoubtedly a serious and potentially life-threatening illness. Cancer chemotherapy has entered a new era of molecularly targeted therapeutics, which is highly selective and not associated with the serious toxicities of conventional cytotoxic drugs. A wide range of heterocyclic ring systems has been studied for the development

of novel chemical entities as a lead molecule in the drug discovery paradigm. Isatin is an endogenous compound identified in humans and their derivatives possess a wide range of biological activities. It possess an indole nucleus having both the keto and lactam moiety as aroused tremendous curiosity due to its diverse biological and pharmacological studies such as CNS depressant activities, sedative agents, anticonvulsant, anticancer, antiHIV , anxiogenic, antimicrobial activity, antitubercular activity.It is an heterocyclic compound capable of crossing the blood brain barrier. As well the Mannich bases of isatin are reported to exhibit broad spectrum of chemotherapeutic properties such as antineoplastic drugs, analgesic drug, antibiotic drugs etc.

During our drug discovery, we have synthesized a series of isatin mannich bases: methyl-4-((substitutedphenyl)[6H-indolo(2,3-b)quinoxalin-6-yl]methylamino)benzoate derivatives **(Figure A)** and tested them against **9** bacterial strains. *In vitro* antibacterial studies revealed that the synthesized isatin derivatives showed more potent and equal activity against tested bacterial stains than the standard employed. In view of the above facts and in continuation of our research work, it was of interest to evaluate the anticancer activity of the synthesized isatin mannich bases. These studies were examined at NATCO Pharma Research labs under the directions of Dr. A.K. S. Bhujang Rao, President R&D, Natco Research Centre in association with Dr. Suneel Natco Research Centre.

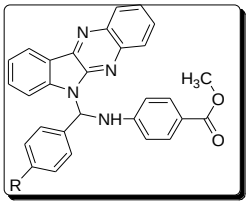


Figure A

R= **4a.** 4- Cl, **4b.** 4-Br, **4c.** 4-No_2, **4d.** 4-OH, **4e.** 4-OH,3-OCH_3, **4f.** 3,4-OCH_3, **4g.** 2,4,6-OCH_3

Published- Chinese Chemical Letters 22 (2011) 567–570.

Indoloquinoxalin derivatives showed more or comparable cytotoxic activity with Erlotinib on lung cancer cell lines, in particular compound **4d** & **4g** exhibited potent

cytotoxic activity on NCIH 292 than Erlotinib. Molecular docking studies indicated that all the tested compounds showed less binding energy with more affinity towards enzyme than the standard (Erlotinib) drug molecule. Therefore, compound **4g** would be a potent anticancer agent with high affinity towards EGFR kinase. Upon encouraging results further studies are under investigation to suggest compound **4g** as novel anti cancer drug.

A series of novel Mannich bases viz., Methyl 4-((4-substituted)(6H-indolo (2,3-b) quinoxalin-6yl)methylamino benzoates **4a-4g** have been synthesized and screened for their antibacterial activity. The antibacterial screening among the newly synthesized compounds showed equal or better than the standard employed (Ciprofloxacin). In particular, activity of compound **4g** was more potent than standard against all the tested strains, while the remaining compounds generally showed inferior or equal activities against all the tested strains.

In continuation of our work, we examined the SAR of the compounds with the increasing donating groups on the final products. The antibacterial activity *in vitro* of compounds **4a-4g** demonstrated that increasing methoxy groups in phenyl ring or with electron donating substituents on the phenyl ring resulted in more antibacterial activity.

Due to electron donating characters of substituents on phenyl ring in compound **4** could obviously affect on pharmacological activity and antibacterial spectrum.

CHAPTER-3:

PART –A:

In chemistry a one-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. This is much desired by chemists because avoiding a lengthy separation process and purification of the intermediate chemical compounds would save time and resources while increasing chemical yield. A sequential one-pot synthesis with reagents added to a reactor one at a time and without work-up is also called a telescoping synthesis.

Knoevenagel condensation is a classic C-C bond formation reaction in organic chemistry.These condensations occur between aldehydes or ketones and active methylene compounds with ammonia or another amine as a catalyst in organic solvents. The Knoevenagel reaction is considered to be a modification of the aldol reaction; the main difference between these approaches is the higher acidity of the active methylene hydrogen when compared to α-carbonyl hydrogen. **Fig 1** illustrates the condensation of a ketone (1) with a malonate compound (2) to form the Knoevenagel condensation product (3), which is then used to form the α, β-unsaturated carboxylic compounds (3) and (4).

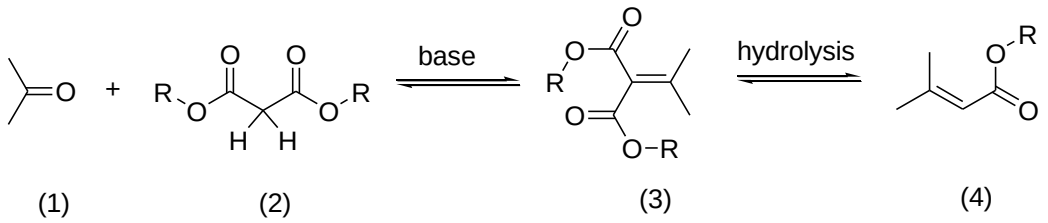


Fig 1. An example of the Knoevenagel reaction.

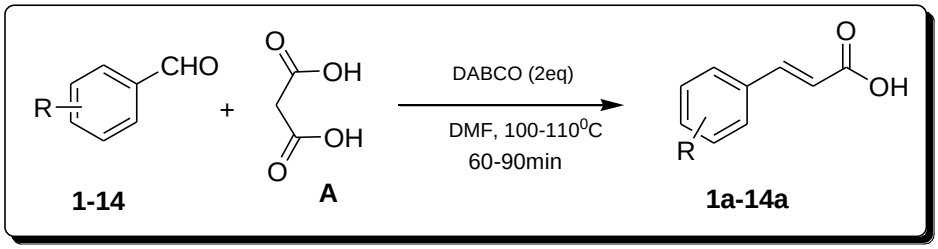
In the present work facile and efficient synthesis of α, β- unsaturated compounds was achieved via Knoevenagel condensation of substituted aromatic aldehydes with malonoic acid and malononitrile employing DABCO as a catalyst. Compounds obtained were of high purity and obtained in lesser time than the reported procedures.

PART –B:

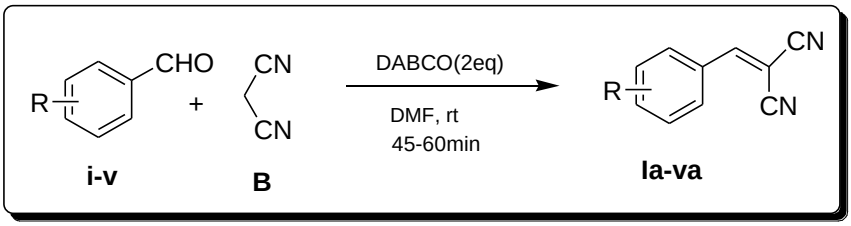
Knoevenagel condensation (Doebner modification) is one of the leading methods for the synthesis of α, β-unsaturated carboxylic acids and nitriles from aromatic aldehydes with active methylene compounds. The classic Knoevenagel-Doebner reaction has been carried out using high amounts of basic solvents like pyridine. The excessive amounts of these solvents damage the environment because of their volatile nature, and also environmentally hazardous. A range of various catalysts have been used for this reaction such as ammonia, primary and secondary amines, lewis acids, surfactants and ionic liquids.

DABCO (1, 4-diazabicyclo [2.2.2] octane) is a diazabicyclic molecule, widely used in organic synthesis and can serve as a weak base and ligand. DABCO has received considerable attention as an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic base catalyst for various organic transformations affording the corresponding products in excellent yields with high selectivity.

In our present work, we report a mild and efficient method for knoevenagel condensation of aromatic aldehydes with active methylene compounds catalyzed by DABCO. Using malonic acid and malononitriles as substrates, the reaction resulted in the formation of substituted *trans*-cinnamic acids and ylidenemalononitriles respectively.



DABCO – catalyzed synthesis of cinnamic acids.



DABCO – catalyzed synthesis of Ylidenemalononitriles.

We have demonstrated a practical application of DABCO catalyzed Knoevenagel condensation reactions, in which even hydroxyl aldehydes can undergo the desired condensation with nearly quantitative yield. In addition, the notable advantages of this procedure are: (a) no need of neutralization; (b) no need of further purification. The reactions are conducted under mild conditions to afford cinnamic acids.

CHAPTER -4:

SECTION –I:

PART –A:

Nanoscience is the study, and nanotechnology is the exploitation, of the strange properties of materials smaller than 100 nanometers (nm) to create new useful objects. This work is made possible by being able to manipulate structures at the size-scale of the atoms. Nanotechnology, or, as it is sometimes called, Engineering at the Molecular Level, is multidisciplinary area of applied science and engineering that deals with the design and manufacture of extremely small components and systems. They are built at the molecular level of matter, are characterized by large surface areas in comparison with their volumes, and have behaviors that are governed by the laws of quantum mechanics.

- **"bottom-up" approach** where materials and devices are built up atom by atom.
- **"top-down" approach** where they are synthesized or constructed by removing existing material from larger entities.

Nanosilver

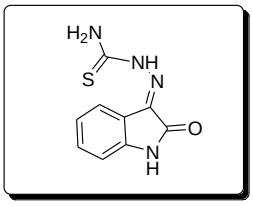
The nanosize results in specific physicochemical characteristics that may differ from those of the bulk substance or particles of larger size. This effect is mainly attributed to high surface area to volume ratio, which potentially results in high reactivity. Because of these specific characteristics the use of substances in nanoform may have advantages over the use of bulk chemicals. Nanotechnology is rapidly expanding and is used in various areas, such as health care, consumer products like cosmetics, ICT, food and feed, environmental health, and agriculture. It is therefore not surprising that many products containing engineered nanoparticles are already available for consumers. One of the substances used in nanoformulation is silver (nano-silver). It has been used since ancient times for jewelry, utensils, monetary currency, dental alloy, photography, explosives, etc. Until the introduction of antibiotics, it was also used for its antiseptic activity, specifically in the management of open wounds and

burns. Due to its antimicrobial properties, silver has also been incorporated in filters to purify drinking water and clean swimming pool water (Agency for Toxic Substances and Disease Registry [ATSDR] 1990, cited in World Health Organization [WHO] 2002). To generate nano-silver, metallic silver has been engineered into ultrafine particles by several methods, including spark discharging, electrochemical reduction, solution irradiation and cryochemical synthesis. Nano-silver particles are mostly smaller than 100 nm and consist of about 20-15,000 silver atoms. Nanoparticles, including nanosilver, may have different shapes, such as spheres, rods, cubes. In addition, nanostructures can be produced as tubes, wires, multifacets, or films. At the nanoscale, the silver particles exhibit deviating physico-chemical properties (like pH-dependent partitioning to solid and dissolved particulate matter) and biological activities compared with the regular metal. This is due to the higher surface area per mass, allowing a larger amount of atoms to interact with their surroundings. Due to the properties of silver at the nanoscale, nano-silver is nowadays used in an increasing number of consumer and medical products. Because silver is a soft white lustrous element, an important use of silver nanoparticles is to give products a silver finish. Still, the remarkably strong antimicrobial activity is the major direction for development of nano-silver products. Of the more than 800 consumer products that contain nanomaterials, roughly 30% are claimed to contain silver particles. Examples are food packaging materials and food supplements, odor-resistant textiles, electronics and household appliances, cosmetics and medical devices, water disinfectants, and room sprays. Some of the applications of nano-silver have resulted in the concern of governments and discussions among the public. An example is the addition of silver nanoparticles to socks to kill the bacteria associated with foot odor. Nano-silver is also used in washing machines because of its antimicrobial activity.

PART –B:

In present work, we report simple and economic method for the synthesis of silver colloid Nanoparticles with controlled size. Silver Nanoparticles were prepared by chemical reduction method. Silver nitrate was taken as a metal precursor and sodium borohydride as a reducing agent. The formation of the silver nanoparticles was

monitored using UV-Vis spectroscopy revealed the formation of silver nanoparticle by exhibiting the typical surface Plasmon absorption maxima at 418-420nm from UV-Vis spectrum. The formed silver nanoparticles were characterized by X-ray diffraction (XRD), Scanning electron microscope (SEM) and FT-IR. The peaks in the XRD pattern are in good agreement with the standard values of the face centered cubic form of metallic silver and no peaks of other impurity crystalline phases were detected. Besides the above studies antibacterial and antidermatophytic activity was studied. The Nanoparticles of silver showed high antibacterial and moderate antidermatophytic activity.



Isatin-3-thiosemicarbazone

Thiosemicarbazones are a class of compounds which has been found to display numerous biological activities. Isatin derived thiosemicarbazones have also been found to show variety of physiological properties. Due to significant pharmacological effects of isatin thiosemicarbazones, there is still an increasing interest in synthesizing and biotesting such compounds. Thiosemicarbazones are mainly used for the preparation of different metal complexes. In our present work, we report the formation and biological activity of the isatin-3-thisemicarbazone capped silver nanoparticles.

The formation of metal nanoparticles has attracted considerable and increasing attention in the field of solid-state chemistry. Because of their small size, the metal nanoparticles exhibit novel material properties that differ from the bulk properties. The unique properties of nanoscopic materials, including their magnetic, optical and electrical properties have been applied to various areas of nanosciences such as nanoelectronics. Metal nanoparticles have been the subject of extensive research for many years because of their anomalous electro-magnetic properties originating from the resonant interaction between light and collective conduction electron oscillations. In the present work, amine coated silver nanoparticles (NPs) are synthesized. Isatin-3-thiosemicarbazone capped

silver Nanoparticles was prepared by chemical reduction method. Chemical reduction in the present work includes a simple chemical reaction of silver iodide and sodium borohydride. By using chemical reduction method silver nanoparticles of 5 – 6nm in size, were formed.

PART –C:

The development of new resistant strains of bacteria to current antibiotics has become a serious problem in public health; therefore, there is a strong incentive to develop new bactericides. Bacteria have different membrane structures which allow a general classification of them as Gram negative or Gram positive. The structural differences lie in the organization of a key component of the membrane, peptidoglycan layer (~2-3 nm) between the cytoplasmic membrane and the outer membrane; gram-positive bacteria lack the outer membrane but have a peptidoglycan layer of about 30nm thick. Silver has long been known to exhibit a strong toxicity to a wide range of microorganisms; for this reason silver-based compounds have been used extensively in many bactericidal applications. Silver compounds have also been used in the medical field to treat burns and a variety of infections. Several salts of silver and their derivatives are commercially employed as antimicrobial agents. Commendable efforts have been made to explore this property using electron microscopy, which has revealed size dependent interaction of silver nanoparticles with bacteria. Nanoparticles of silver have thus been studied as a medium for antibiotic delivery and to synthesize composite for use as disinfecting filters and coating materials. However, the bactericidal property of these nanoparticles depends on their stability in the growth medium. Since this imparts greater retention time for bacterium- nanoparticle interaction. There lies a strong challenge in preparing nanoparticles of silver stable enough to significantly restrict bacterial growth.

Isatin-3-thiosemicarbazone capped silver nanoparticles and Isatin-3-thiosemicarbazone was tested for antimicrobial assay on Human pathogenic organisms which were isolated from infected patients. The antimicrobial screening of newly synthesized silver nanoparticles showed equal or better activity than the standard employed. The synthesized silver nanoparticles showed equal or better activities on all

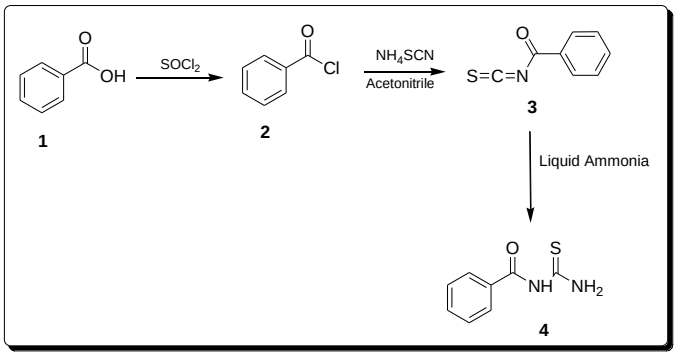
tested microorganisms i.e, *Salmonella typhi, Vibrio cholerae, Shigella dysenteriae, Eterococcus faecalis* and *Trichophyton rubrum*. The Minimum Inhibitory Concentration of silver nanoparticles was equal to the Minium Inhibitory Concentration of antibiotics employed i.e, Ciprofloxacin and Griseofulvin but in case of *Shigella dynsenteriae* the Minimum Inhibitory Concentration of silver nanoparticles was more than the Minimum Inhibitory Concentration of the antibiotic employed.

SECTION –II

PART –A:

In the present work we synthesized silver nanoparticles by chemical reduction method using silver nitrate as metal precursor and sodium borohydrate as a reducing agent. The formation of the silver nanoparticles was monitored using UV –Visible absorption spectroscopy. Further the formed silver nanoparticles were characterized by X-ray diffraction (XRD), Scannning electron microscope (SEM) and FT-IR. The peaks in the XRD pattern are in good agreement with the standard values of the face-centered-cubic form of metallic silver and no peaks of others impurity crystalline phases were detected. In addition to the above properties we have also studied the antibacterial and antidermatophytic activity of the formed silver nanoparticles and they showed high antibacterial and moderate antidermatophytic activity.

Replacement of oxygen atom in urea by sulphur atom produces thiourea which has been successfully used in many diseases. Mitchell *et al*., explained that 'Thiourea' the sulphur analogue of urea has been known for over a century and a quarter during which time it has found a variety of uses, some within the biological field. Most noted of these have been their employments as a plant growth stimulator to break bud dormancy and increase crop yield and more recently as a therapeutic agent to treat thyroid dysfunction. Physiological effects of thiourea are closely related with those urea groups are responsible for the origin of biological spectrum in the compound.



N-benzoylthiourea synthesis

N-benzoylthiourea or N-carbamothioylbenzamide capped silver nanoparticles was prepared by chemical reduction method. Silver nanoparticles of 6-8nm in size were formed. Chemical reduction process includes a simple chemical reaction of silver iodide and sodium borohydride (silver nitrate is used as a metal precursor).

PART –B:

The bactericidal effect of silver ions on microorganisms is very well known; however, the bactericidal mechanism is only partially understood. It has been proposed that ionic silver strongly interacts with thiol groups of vital enzymes and inactivates them. Experimental evidence suggests that DNA loses its replication ability once the bacteria have been treated with silver ions. Silver ions have been demonstrated to be useful and effective in bactericidal applications, but due to the unique properties of nanoparticles nanotechnology presents a reasonable alternative for development of new bactericides.

N-benzoylthiourea capped silver nanoparticles showed large zones of inhibition on all human pathogenic bacteria compared to standard. Hence, from the results it is considered that the synthesized silver nanoparticles showed potent (inhibitory) activity than the antibiotic employed. Whereas, the zone of inhibition on dermatophyte by N-benzoylthiourea capped silver nanoparticles was equal when compared to standard.

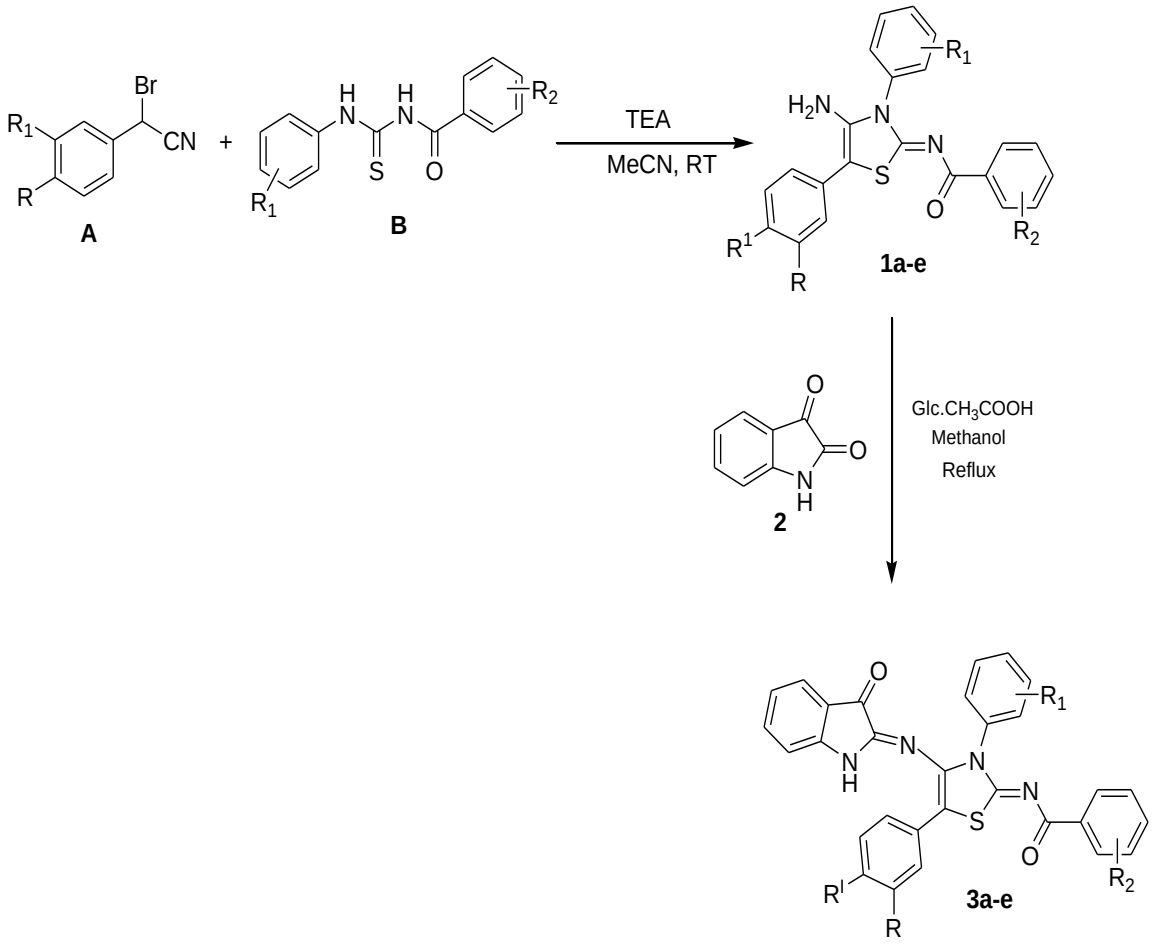
The Minimum Inhibitory Concentration of N-benzoylthiourea capped silver nanoparticles was equal to the Minimum Inhibitory Concentration of antibiotics (standard) employed. However, in case of *Vibrio cholerae, Shigella dysenteriae, Enterococcus*

faecalis the Minimum Inhibitory Concentration of synthesized N-benzoylthiourea capped silver nanoparticles showed better MIC value (1µg/ml) than the standard (10µg/ml).

CHAPTER -5:

Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry. A literature survey identified several isatin derivatives in the development phase as potential new drugs. A variety of biological activities are associated with isatin including CNS activities as potentiation of pentobarbitone induce nercosis, analgesic, anticonvulsant, antidepressant, antiinflammatory, antimicrobial, and effects on the central nervoussystem. Isatins are capable of crossing the blood–brain-barrier. Isatin, a heterocyclic compound was identified in animals as a major component of the endogenous monoamine oxidase inhibitor. The various substituents at 3rd position of the isatin which were reported various substituted phenyl ring moieties, heterocyclic rings and aliphatic system. Isatin (1*H*-Indole-2,3-dione) is one of the most promising new class of heterocyclic molecules having many interesting activity profiles and well-tolerated in human subjects.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which includes the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form am imine or Schiff base.



Synthetic scheme for compound 3

In summary, we have synthesized isatin schiff bases from 2-imino-4-aminothiazoles which inturn derived from unsymmetrical thioureas. The synthesized compounds were obtained in purer form. A Schiff base of isatin is a field that is being noticed. Schiff base of isatins are considered privileged because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. These compounds have a variety of applications including clinical, analytical and industrial. Schiff bases of isatins were reported to possess broad-spectrum of anticonvulsant, anxiety activities and other biological activity. Further the pharmacological activities of the synthesized compounds will be examined and expected to show potent activity on the tested species.